In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: August 30, 2019

JAMILEH BERENJI and BAHMAN YOUSEFI on behalf of S.Y.,	
Petitioners,	PUBLISHED
v.	No. 14-699V
SECRETARY OF HEALTH AND HUMAN SERVICES,	Special Master Gowen
Respondent.	Entitlement; Off-Table Injury; Significant Aggravation; Influenza; Measles-Mumps-Rubella; Varicella; Prevnar; Evans Syndrome.

Mark T. Sadaka, Mark T. Sadaka, LLC, Englewood, NJ, for petitioners.
Sarah C. Duncan, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

On August 4, 2014, Jamileh Berenji and Bahman Yousefi ("petitioners"), on behalf of their minor child S.Y., filed a petition for compensation in the National Vaccine Injury Compensation Program.[2] S.Y. received influenza ("flu"), measles-mumps-rubella ("MMR"), varicella, and pneumococcal conjugate ("Prevnar") vaccinations on October 17, 2011. Petitioners allege that those vaccinations significantly aggravated S.Y.'s pre-existing asymptomatic Evans syndrome and that significant aggravation included a multitude of clinical phenomena including but not limited to autoimmune hepatitis and pulmonary veno-occlusive

[1] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this opinion contains a reasoned explanation for the action in this case, I am required to post it on the website of the United States Court of Federal Claims. The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. **This means the opinion will be available to anyone with access to the Internet.** Before the opinion is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). An objecting party must provide the court with a proposed redacted version of the opinion. *Id.* **If neither party files a motion for redaction within 14 days, the opinion will be posted on the court's website without any changes.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-1 to 34 (2012) ("Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

disease (PVOD). Based on a full review of all of the evidence and testimony presented, I find that petitioners have not established entitlement to compensation.[3]

I. Procedural History

On August 4, 2014, petitioners timely filed their claim concerning the flu, MMR, varicella, and Prevnar vaccinations received by S.Y. on October 17, 2011. Petition (ECF No. 1) at Preamble, ¶ 4. Petitioners alleged that these vaccinations either caused-in-fact, or in the alternative, significantly aggravated S.Y.'s Evans syndrome[4] and resultant injuries. *Id.* at Preamble. During an initial status conference on October 22, 2014, respondent represented that his initial position was to defend the claim rather than to pursue a settlement. I agreed that expert reports would be necessary to understand the complex issues concerning S.Y.'s medical condition and the timing in this case. Scheduling Order (ECF No. 10).

Petitioners filed a report from Dr. M. Eric Gershwin, M.D.[5], who opined in support of vaccine causation. Petitioners' Exhibits ("Pet. Ex.") 8 (his report), 9 (curriculum vitae). In response, respondent filed a report from Dr. Mehrdad Matloubian, M.D.[6] Respondent's

[3] Pursuant to Section 13(a)(1), in order to reach my decision, I have considered the entire record, including all of the medical records, expert testimony, and literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

[4] As discussed below, Evans syndrome is a very rare condition. However, it has been the subject of at least four prior claims. *See Isom v. Sec'y of Health & Human Servs.*, No. 97-770V, 1998 WL 835519 (Fed. Cl. Spec. Mstr. Nov. 3, 1998) (denying entitlement); *Cohen v. Sec'y of Health & Human Servs.*, No. 94-353V, 1998 WL 408784 (Fed. Cl. Spec. Mstr. July 1, 1998) (denying entitlement); *Mason v. Sec'y of Health & Human Servs.*, No. 14-487V, 2017 WL 3814643 (Fed. Cl. Spec. Mstr. Aug. 4, 2017) (approving the parties' stipulation awarding compensation to petitioners); *Bucci v. Sec'y of Health & Human Servs.*, No. 14-699V, 2019 WL 1891809 (Fed. Cl. Spec. Mstr. Mar. 27, 2019) (the undersigned's opinion denying entitlement). Although I have reviewed these past opinions on Evans syndrome, they are generally not discussed in the present opinion because I have reached my own independent conclusion based on the evidence submitted in the case before me.

[5] Dr. Gershwin obtained a bachelor's degree in mathematics from Syracuse University in 1966 and an M.D. from Stanford University in 1971. Pet. Ex. 9 at 1. He completed an internship and residency at Tufts-New England Medical Center, then served as a clinical associate in immunology at the National Institutes of Health. *Id.* at 2. In 1975, he became employed at Stanford University, where he has received various titles and honors relating to immunology, rheumatology, and allergy. He is currently the Jack and Donald Chia Professor and a Distinguished Professor of Medicine in the divisions of Rheumatology/ Allergy and Clinical Immunology at Stanford. *Id.* at 1-2. He is board-certified in internal medicine, allergy and clinical immunology. *Id.* at 2. He has conducted research and published on many subjects including autoimmunity, autoimmune thrombocytopenia (ITP), autoimmune hepatitis, and autoimmune lung conditions. *See generally* Pet. Ex. 9; Tr. 5-8. Dr. Gershwin has personally treated one individual with ITP, but no one with Evans syndrome. Tr. 5-6. I admitted Dr. Gershwin as an expert in rheumatology, immunology, and clinical immunology. Tr. 9.

[6] Dr. Matloubian obtained a bachelor's degree in biochemistry from the University of California – Los Angeles in 1988, followed by an M.D. and a Ph.D. in virology from the same institution in 1996. Resp. Ex. B at 1. He is board-certified in internal medicine and rheumatology. *Id.* He completed an internship and a residency, followed by a fellowship in rheumatology and a post-doctoral fellowship, all at the University of California – San Francisco (UCSF). *Id.* Since 2001, he has also been teaching at UCSF, where according to his curriculum vitae, he is an Associate Adjunct Professor in medicine. *Id.* at 2. He spends one month each year attending rheumatology patients at UCSF and operates his own clinic where he sees patients one full day each week. *Id.* at 2-3; Tr. 145-46. At the hearing, Dr. Matloubian reported that in 2017, he became involved in a "new clinical endeavor" at UCSF called the Moffitt-Long Medicine Consult Service, in which experts in different fields, together, would look at patients who

("Resp.") Ex. A (first report), B (curriculum vitae). Respondent also filed a Rule 4(c) report (ECF No. 17). On April 10, 2015, I held a status conference pursuant to Vaccine Rule 5 and set deadlines for both parties to file supplemental expert reports. Scheduling Order (ECF No. 23).

Petitioners filed a second report from Dr. Gershwin. Pet. Ex. 11. Respondent filed a second report from Dr. Matloubian. Resp. Ex. C. On September 22, 2015, I held another status conference in which I indicated that petitioners should further develop how the vaccines at issue could and did significantly aggravate S.Y.'s condition. I directed both parties to identify dates for an entitlement hearing but also to pursue informal resolution of the claim. Scheduling Order (ECF No. 29). Petitioners then filed a third report from Dr. Gershwin. Pet. Ex. 12.

Informal resolution was complicated by the existence of a significant Medicaid lien related to S.Y.'s medical treatment and the difficulty of separating the expenses of his preexisting Evans syndrome from the expenses related to the alleged significant aggravation. I emphasized that there remained significant litigative risk on both sides but agreed to proceed to an entitlement hearing. *See, e.g.*, Status Report filed February 3, 2016 (ECF No. 39); Scheduling Order issued on March 23, 2016 (ECF No. 44). In spring 2016, petitioners filed medical records pertaining to S.Y.'s continued medical treatment. Pet. Exs. 108, 109. In summer 2016, respondent filed the first report of Dr. Joan Cox Gill, M.D.[7] Resp. Ex. D. In fall 2016, petitioners filed a motion for interim attorneys' fees and costs (ECF No. 50), which was granted. Decision (ECF No. 54).

In May 2017, petitioners filed a pre-hearing brief (ECF No. 61), followed by respondent (ECF No. 63). A one-day entitlement hearing was held on August 14, 2017, in San Francisco, California. Post-Hearing Order filed August 17, 2017 (ECF No. 86); Transcript filed August 30, 2017 (ECF No. 88). I heard testimony from petitioner Jamileh Berenji as well as Dr. Gershwin, Dr. Matloubian, and Dr. Gill. At the conclusion of the hearing, I encouraged the parties to revisit the possibility of settlement, focusing on reducing the Medicaid lien to the costs attributable to

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are "hospitalized with multiple organ diseases and complex diseases that have no diagnosis yet." Tr. 146. Dr. Matloubian devotes approximately 50% of his time on research and publication. Tr. 147-49. I admitted Dr. Matloubian as an expert in rheumatology with specialized expertise in autoimmune diseases and immunology. Tr. 148.

[7] Dr. Gill obtained a bachelor's degree in science from St. Norbert College in 1965 followed by an M.D. from the Medical College of Wisconsin in 1976. Resp. Ex. E at 1. Dr. Gill then completed an internship and residency in Pediatrics at Milwaukee Children's Hospital, followed by a fellowship in Pediatric Hematology-Oncology at the Medical College of Wisconsin and the Blood Center of Southeastern Wisconsin, which houses the university's comprehensive center for bleeding disorders. *Id.* at 1; Tr. 91. At the blood center, she served as the director for approximately 30 years, then became an investigator conducting research and seeing patients on clinical trials. Resp. Ex. E at 2; Tr. 91. She was also affiliated with the university for over 30 years, rising to the position of Professor of Medicine, Pediatrics, and Population Health – Epidemiology until she stepped down on June 30, 2017 (approximately one month before the entitlement hearing in this case). Resp. Ex. E at 2; Tr. 91. She had active board certifications in general pediatrics as well as pediatric hematology and oncology. Dr. Gill stated that she had personally treated about five patients with Evans syndrome and not infrequently consulted with her colleagues and other institutions about other patients with the disease. Tr. 92. Resp. Ex. E at 4; Tr. 93. I admitted Dr. Gill as an expert in pediatrics and pediatric hematology. Tr. 95. Sadly, between the hearing and the issuance of this decision, Dr. Gill passed away. The undersigned would like to express his condolences for Dr. Gill's passing as well as gratitude for her service in many complex cases in the Vaccine Program.

significant aggravation by the vaccines at issue. Post-Hearing Order filed August 17, 2017 (ECF No. 86). After further settlement efforts, the parties reported that respondent was not amenable to settlement. The parties agreed to file simultaneous post-hearing briefs. Joint Status Report filed November 2, 2017 (ECF No. 91). Those were received on March 30, 2018. Petitioners' Post-Hearing Brief (ECF No. 97); Respondent's Post-Hearing Brief (ECF No. 98). Accordingly, this matter is now ripe for adjudication.

II. General Legal Standards for Adjudication[8]

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. No. 908 at 3, *reprinted in* 1986 U.S.C.C.A.N. at 6287, 6344).

A petitioner bears the burden of establishing his or her entitlement to compensation from the Vaccine Program. The burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). A petitioner may prevail by proving either that (1) the vaccinee suffered an injury listed on the Vaccine Injury Table with onset beginning within a corresponding time period following receipt of a corresponding vaccine (a "Table Injury"), for which causation is presumed or that (2) the vaccinee suffered an injury that was actually caused by a vaccine. Under either method, however, the petitioner must also show that the vaccinee "suffered the residual effects or complications of the illness, disability, injury, or condition for more than six months after the administration of the vaccine." Section 11(c)(1)(D)(i).

In the present case, petitioners do not allege a Table injury, thus, they bear the burden of establishing actual causation. Furthermore, petitioners acknowledge that S.Y. had Evans syndrome before the vaccinations at issue. Therefore, they allege that the vaccinations significantly aggravated S.Y.'s condition. Petitioners' Post-Hearing Brief at 1.

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). In *Loving*, the United States Court of Federal Claims established the governing six-part test for off-Table significant aggravations. Petitioner must prove by a preponderance of the evidence:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory

[8] Decisions of special masters and the U.S. Court of Federal Claims (some of which are referenced in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

> causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this as the proper legal standard for significant aggravation claims brought under the Vaccine Act). *Loving* prongs four, five, and six are derived from the Federal Circuit's test for off-Table actual causation cases. *Althen v. Sec'y of Health & Human Servs.*, 17 F.3d 374 (Fed. Cir. 1994).

"One part of an analysis of a significant aggravation claim is evaluating whether the vaccine made the person worse than the person would have been but for the vaccination. In doing so, the natural course of the disease must be considered." *Locane v. Sec'y of Health & Human Servs.*, No. 99-589V, 2011 WL 3855486 at *10 (Fed. Cl. Spec. Mstr. Feb. 17, 2011), *motion for review denied*, 99 Fed. Cl. 715 (2011), *aff'd*, 685 F.3d 1375 (Fed. Cir. 2012); *see also Hennessey v. Sec'y of Health & Human Serv.*, No. 01-190V, 2009 WL 1709053, at *41-42 (Fed. Cl. Spec. Mstr. May 29, 2009), *motion for review denied*, 91 Fed. Cl. 126 (2010).

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met their burden of proof. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009); *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

Once a petitioner fulfills the six *Loving* prongs, the burden of persuasion shifts to respondent to show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994); § 13(a)(1)(B).

In Vaccine Act cases, expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95). In Vaccine Program cases, these factors are used in the weighing of the scientific evidence actually proffered and heard. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66–67 (Fed. Cl.

2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in Vaccine Program cases has routinely been upheld. *See, e.g., Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 742–45 (2009).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

III. Analysis[9]

1. *Loving* Prong One: S.Y.'s condition before the October 17, 2011 vaccinations.

This prong requires an "assess[ment] of the person's condition prior to administration of the vaccine[s]." *Loving*, 86 Fed. Cl. at 143.

The medical records reflect that S.Y. was born at term in October 2010. His APGAR score was 8/10 at 1 minute and 9/10 at 5 minutes. Pet. Ex. 1 at 35. *See generally* Pet. Ex. 1. During the first year of life, he attended several well-baby evaluations with Dr. Patricia Lee at Sutter Health in Santa Clara, California. Dr. Lee recorded that he was developing normally and was generally healthy except for poor sleep hygiene and minor penile adhesions. He was meeting milestones and there was no notation of bruising or bleeding. On June 13, 2011, Dr. Lee saw S.Y. for a three-day history of cough, which she assessed as an upper respiratory

[9] Rather than providing a separate summary of the relevant facts before and after the vaccines at issue (drawing from the medical records and the fact witness testimony), I find it appropriate to present that information here, under *Loving* prongs one and two.

infection and which apparently resolved without further medical attention. Pet. Ex. 4 at 18-37.[10] There were no further medical appointments before the vaccinations at issue.

2. *Loving* Prong Two: S.Y.'s condition after the October 17, 2011 vaccinations.

This prong requires an assessment of "the person's current condition (or the condition following the vaccination[s] if that is also pertinent)". *Loving*, 86 Fed. Cl. at 143.

On October 17, 2011 at approximately 4:10 p.m., S.Y. and his mother presented for his twelve-month well-child examination with Dr. Lee. She recorded that apart from S.Y.'s minor penile adhesions, he appeared normal and healthy. S.Y. received his first MMR vaccination and first influenza vaccination in his left thigh, as well as his first varicella vaccination and his fourth pneumococcal vaccination in his right thigh. Pet. Ex. 4 at 37-42; Pet. Ex. 6 at 100-01. Dr. Lee recorded the mother's history of anemia, then advised that S.Y. undergo a hemogram (complete blood count). Pet. Ex. 4 at 41-42.[11] S.Y.'s blood specimen was obtained at approximately 4:53 p.m. *Id.* at 57. The platelet count was found to be 17,000 K/uL (significantly low, compared to reference range of 150,000 – 400,000/uL); hemoglobin count was 10.7 g/dL (slightly low, compared to reference range of 11.0 – 14.5 g/dL); hematocrit level was 31% (low, compared to reference range of 33.0 – 43.5%) and white blood cell count was 8.7 K/uL (normal, within reference range of 6.0 – 17.5 K/uL). *Id.*

S.Y.'s mother was notified that his blood counts were low and she brought him back to Sutter Health for repeat testing as recommended, which was obtained the next day, October 18, 2011, at 11:05 a.m. Platelets were "markedly decreased" at 6,000/uL. There were less dramatic decreases in hemoglobin at 10.6 g/dL; hematocrit at 30.5%; and white blood cells at 6.3 K/uL. Pet. Ex. 4 at 57. That day at 2:00 p.m., reticulocytes[12] were at 1.8 Hcf (above the reference range of 0.5 – 1.5 Hcf). Pet. Ex. 2 at 884.

On October 18, 2011, in light of the confirmed thrombocytopenia and slight hemolytic anemia, Dr. Lee referred S.Y. to Lucile Packard Children's Hospital at Stanford University

[10] His mother recalled that S.Y. was a "very happy, healthy boy" during the first year of life. Pet. Ex. 10 ¶¶ 5, 6; Tr. 67.

[11] *See also* Pet. Ex. 2 at 870 (October 18, 2011 record by hematologist-oncologist Dr. Michael Friedberg noting that the mother was anemic and taking iron supplements); *id.* at 852 (October 29, 2011 record by infectious disease specialist Dr. Laura Dyner that the mother "had been advised by a physician relative in Iran that children should take iron to aide [sic] their growth" and she had asked Dr. Lee for bloodwork to evaluate S.Y. for anemia). In her affidavit, the mother recalled asking Dr. Lee to do the bloodwork to determine whether S.Y. needed to take iron or multivitamin supplements. Pet. Ex. 10, ¶ 7.

However, at the entitlement hearing, the mother testified that the bloodwork was required for a form his pediatrician needed to complete for the Special Supplement Nutrition Program for Women, Infants, and Children. She also stated that she developed anemia and had to start taking iron supplements only after having stomach bypass surgery to lose weight. She may have taken iron supplements beforehand in connection with a heavy menstrual cycle. Tr. 64-66.

[12] A reticulocyte is an immature red blood cell. *Dorland's Illustrated Medical Dictionary* (32nd ed. 2012) [hereinafter "*Dorland's*"] at 644, 1631.

(LPCH). S.Y. and both parents presented to Lucile Packard the same day. Dr. Michael Friedberg recorded:

> On review of systems with us, he was noted to have a fall approximately one week ago where he had a nosebleed that lasted approximately 30 seconds which resolved on its own without any pressure.[13] Of note, Mom also noticed that he has a few bruises notably on his forehead and his right forearm which Mom thought has been secondary to his ability to walk around and normal toddler bruising…. Otherwise he has been doing well without any other symptoms.[14]

Pet. Ex. 2 at 869. Dr. Friedberg recorded the mother's report that she was anemic and taking iron. *Id.* at 870. Dr. Friedberg's assessment was "severe thrombocytopenia and anemia. Based on our laboratories it appears that he currently only has one cell line down with the platelets…. [O]ur running diagnosis is ITP [immune thrombocytopenia]." *Id.* Dr. Friedberg recommended follow-up in one week. *Id.* One day, later, on October 19, 2011, Dr. Friedberg learned that a Coombs test was positive and had another brief consultation with the parents advising that S.Y.'s diagnosis had been changed to Evans syndrome, "an autoimmune process that results in hemolytic anemia and thrombocytopenia." *Id.* at 850. He advised the parents to monitor for changing symptoms and signs including "increased bruising, bleeding, pallor, jaundice, and poor feeding or energy" and to "monitor [S.Y.] closely to prevent any traumas, especially to the head." *Id.*

After the diagnosis of Evans syndrome was confirmed on October 19, 2011, the next medical record was on October 23, 2011, when S.Y. presented for emergency attention following a one-day history of vomiting and diarrhea, as well as a fever which had risen to approximately 104 degrees Fahrenheit. He received antibiotics. On October 25, 2011, S.Y. presented to Dr. Lee with "persistent fever" which was measured at 102 degrees Fahrenheit. He also needed a second dose of ceftriaxone (antibiotic), which Dr. Lee administered. Dr. Lee recorded: "Parents understandably very devastated by his recent diagnosis and mom still very concerned that his recent 12-month vaccines, most notably, the MMR, was the etiology of his current condition. Discussed that while the stress of the vaccines may have triggered the disease to surface, it certainly was not the cause of his Evan[s] syndrome." Consistent with the mother's report, on physical examination, Dr. Lee recorded "several purplish ecchymoses[15] on lower extremities, the largest one on his left upper thigh measuring 7 cm in diameter." Dr. Lee's assessment was "fever, likely viral etiology or possibly even due to his recent vaccines[…] [c]annot rule out underlying bacterial etiology" and Evans syndrome. Pet. Ex. 4 at 43-44.

On October 25, 2011, S.Y. established care with pediatric hematologist-oncologist Dr. Duda, who also recorded the fever and diagnosis of Evans syndrome. His bloodwork was still

[13] At the entitlement hearing, the mother testified that she did not recall the nosebleed or bruises before the vaccination "at all." Tr. 69.

[14] The mother testified that S.Y. began having bruises "a day or two after the vaccine." Tr. 69.

[15] An ecchymosis (plural: ecchymos*es*) is "a small hemorrhagic spot, larger than a petechia, in the skin or mucous membrane forming a non-elevated, rounded or irregular, blue or purplish patch." *Dorland's* at 1829.

outside of normal ranges with platelets at 11,000 K/uL; hemoglobin at 9.8 g/dL; hematocrit at 27.2%; and white blood cells at 3.0 K/uL. Pet. Ex. 2 at 866-67, 873.

In a follow-up on October 28, 2011, Dr. Duda recorded that S.Y.'s fever had resolved. However, he had developed a diffuse macular papular rash. Her impression was: "autoimmune pancytopenia, probably post-viral." Dr. Duda "discussed with Mom the possibility that if this [febrile illness with rash] is indeed measles disease, and if it is vaccine-related, this rare occurrence, concurrent with an apparently autoimmune pancytopenia, may raise a question of a previously undiagnosed immune deficiency." *Id.* at 860-61.

That same day, a blood smear showed reactive lymphocytes, which prompted the technician to inquire as to whether S.Y. had recently received the MMR vaccine. The hematology-oncology team recommended that S.Y. be admitted for observation. *Id.* at 853, 875. Upon leaving for the hospital, S.Y. had an episode of eye-rolling and jerking movements in both arms. *Id.* at 853. The family recalled that this apparent seizure lasted approximately two to three minutes and S.Y. did not return to baseline until approximately 10 minutes afterwards, after which EMS arrived. *Id.* at 790-91, 852-59. S.Y. was admitted to LPCH due to tonic-clonic seizures associated with fever and rash. *Id.* at 855. Head CT, EEG, and lumbar puncture were normal. *Id.* Repeat bloodwork revealed that his platelets had decreased further to 6 K/uL. Hemoglobin was slightly lower at 9.7 g/dL as well as hematocrit at 26.9%. White blood cells had increased but were still low at 8.0 K/uL. *Id.* at 887. The next day, October 29, S.Y. received ceftriaxone (antibiotic) and intravenous immunoglobulin (IVIg). *Id.* at 854.

On October 29, pediatric infectious disease specialist Dr. Laura Dyner recorded that S.Y.'s vaccinations could not have caused his anemia and thrombocytopenia, which were documented less than one hour afterwards. However, "it is possible that [S.Y.'s] fever and rash (and less likely, afebrile seizure) were caused by MMR, and that these are unrelated to the cause of his underlying bone marrow suppression/ autoimmune hemolytic anemia." *Id.* at 856.

After evaluating S.Y. on October 31, immunologist Dr. David Lewis wrote: "It is possible that he had two distinct processes happening simultaneously." *Id.* at 784. First, Evans syndrome probably represented a "true autoimmune process." *Id.* Second, the MMRV vaccine may have caused a self-limited febrile seizure episode. As Dr. Lewis wrote:

> Early findings from an ongoing CDC study show that children who get an MMRV vaccine may be twice as likely to have a febrile seizure 7-10 days after getting the shot than children who get MMR and varicella vaccines (2 shots) at the same health care visit. During the 7-10 days after vaccination, about one additional febrile seizure would be expected to occur among every 2,000 children vaccinated with MMRV vaccine, compared with children vaccinated with MMR and varicella administered at the same visit. Both measles and varicella are live virus vaccines, but measles is much more attenuated than the varicella vaccine, although measles has been more associated with encephalitis than varicella. Given his quick recovery after his two seizures and the lack of any neurological findings afterward, it is unlikely that he actually had an encephalitis.

Id. at 785. S.Y. was discharged on prednisone (a steroid) on November 2, 2011. *Id.* at 799.

On November 4, 2011, S.Y. was seen by Dr. Wendy Wong, a pediatrician, for a follow-up after his hospitalization. She recorded the parents' report that S.Y. was doing well without further rash, fever, or seizure activity. *Id.* at 765. She wrote: "[A]fter extensive workup by Infectious Disease and Immunology, the general thought is that [S.Y.] developed some rare but known complication from his measles, mumps, and rubella vaccine which included fever, a rash, and seizure…. It is therefore likely that [S.Y.] had two different processes that occurred at the same time. We also believe that [S.Y.'s] Evans syndrome did not stem from his measles, mumps, and rubella, as his thrombocytopenia was noted just one hour after his vaccine." *Id.* at 766.

The LPCH records reflected that reticulocytes rose to 8.2 Hcf by November 4, 2011 and to 10.9 Hcf by November 8, 2011. *Id.* at 776, *compare to id.* at 884 (reflecting reticulocytes at 1.8 Hcf on October 18, 2011).

On November 10, 2011, Dr. Duda noted S.Y.'s hospitalization and that his "apparent vaccine-related illness has since resolved." *Id.* at 863. S.Y. also had several days of significant diarrhea "of unclear etiology, but it appears to be self-resolving." *Id.* at 864.

On December 27, 2011, S.Y. presented again to LPCH. Earlier in December, his doctors had tried to taper him off steroids. However, his urine appeared darker than usual and he was paler with some yellowness to his skin and eyes. His bloodwork showed low hemoglobin and platelets, for which he was hospitalized. A steroid pulse was not effective. On December 31, 2011, S.Y. started a five-day course of IVIg which was associated with improved blood counts. He was discharged with steroids on January 5, 2012. *Id.* at 714-18.

Due to continued thrombocytopenia on oral steroids, he received four infusions of Rituximab (an immunosuppressant) between February 13 and March 15, 2012. *Id.* at 110. However, due to a lack of sustained response, on April 17, 2012, he was started on cyclosporine (another immunosuppressant). *Id.*

On June 1, 2012, S.Y. experienced an episode of non-responsiveness and shaking lasting approximately 15 minutes, which possibly represented a seizure. His parents called paramedics, who administered Versed (a benzodiazepine/ sedative) and brought him to the emergency room at O'Connor Hospital. S.Y.'s blood counts were low. The seizure was suspected to be an adverse reaction to cyclosporine. Pet. Ex. 3 at 30-54. He was then transferred to LPCH, where neurologists Dr. Donald Olson and Dr. Jonathan Lopez noted that back in November 2011, S.Y. "almost certainly" had "an acute *provoked* seizure following the MMR vaccine." Pet. Ex. 2 at 474 (emphasis added). In contrast, June 1, 2012 represented S.Y.'s first "unprovoked" seizure. *Id.* Later in June 2012, S.Y. experienced another seizure and an MRI of his brain showed some cortical dysplasia. Cyclosporine was discontinued and he was started on Keppra (an anti-seizure medication). Pet. Ex. 3; Pet. Ex. 2 at 456-57; Pet. Ex. 5 at 936.

On July 17, 2012, S.Y. was started on CellCept (another immunosuppressant). Pet. Ex. 2 at 110. From September 8-11, 2012, he was admitted to LPCH due to rectal bleeding. During this hospitalization, he received a platelet transfusion and IVIg. *Id.* at 412-13.

On February 12, 2013, "T and B cell subsets…. were normal…. indicating that [S.Y.] ha[d] recovered from the Rituximab therapy in February - March 2012." Pet. Ex. 2 at 121.

Also on February 12, 2013, CellCept was discontinued due to rising alkaline phosphatase levels. Afterwards, S.Y. was increasingly fatigued and less interested in playing and ambulating. A non-productive cough present since November 2012 seemed to worsen in frequency and productivity. *Id.* at 110-33.

On February 22, 2013, S.Y. underwent a bone marrow biopsy which was "suspicious for malignancy." *Id.* at 98. Due to S.Y.'s increased difficulty breathing and an oxygen saturation of 85%, he was admitted to LPCH. He was started on supplemental oxygen – beginning at 15L saturation by face mask, then changed to 2L by nasal tubes. *Id.* at 98-99.

On March 1, 2013, a repeat bone marrow biopsy showed:

> While platelets are markedly decreased with circulating giant forms, the bone marrow aspirates and biopsy sections show an abundant megakaryocytic hyperplasia, including small immature forms. The finding of hyperplastic megakaryocytes suggests the etiology of the thrombocytopenia is not poor platelet production, but rather peripheral destruction and/or sequestration. Both red cell and megakaryocyte/platelet findings are consistent with immune-mediated destruction of red cells and platelets and have been described in Evans syndrome.

Id. at 139.

On March 7, 2013, S.Y. was transferred to the LPCH pediatric intensive care unit (PICU) after he developed seizure-like activities with tonic-clonic movements and ineffective breathing. He was stabilized with non-invasive respiratory support. Upon arrival to the PICU, S.Y. was found to have positive anti-nucleotide antibodies (ANA) for the first time. He also had complements obtained that were significantly low: C3 was 60 and C4 was 6.2. *Id.* at 98-99.

An EEG showed diffuse slowing but no seizure activity. After he experienced another seizure lasting 20 minutes on March 9, 2013, he was started on Keppra and had no further seizures for the remainder of the hospitalization. On March 28, 2013, lung biopsy histologic findings confirmed a diagnosis of pulmonary veno-occlusive disease (PVOD) (which related back to and explained the respiratory problems which had begun in mid-February 2013). S.Y. was discharged with supplemental oxygen on April 8, 2013. Pet. Ex 5 at 133-42.

In early August 2013, the parents stopped giving S.Y. Keppra because they were overwhelmed by the number of medications he was taking. Pet. Ex. 5 at 8282-84, 8575-80. S.Y.'s ANA was positive again in August 2013. Pet. Ex. 5 at 8051, 9254-57. Also in August 2013, he was hospitalized for eight days due to a pulmonary infection that exacerbated his PVOD. He received platelets and steroids. *Id.* at 8575-81.

On September 26, 2013, S.Y. was again hospitalized for worsening jaundice, difficulty breathing, and high levels of bilirubin and transaminases (liver enzymes). Tests for rhinovirus and parainfluenza were positive. A liver cell biopsy showed syncytial giant cell hepatitis, suggestive of autoimmune hepatitis. He received additional platelets and steroids. He was discharged 96 days later on December 26, 2013. *Id.* at 747-49, 898-906; Pet. Ex. 6 at 67-68.[16]

On April 11, 2014, S.Y. began taking Tacrolimus (another immunosuppressant) and inhaled pentamidine (an antimicrobial medication). Pet. Ex. 5 at 1573-74. Whole genetic exome sequencing completed on May 24, 2014 found no "genetic evidence for either a primary immunodeficiency and/or autoimmune disease" to explain S.Y.'s condition. *Id.* at 375-76.

From May 25 to June 3, 2014, S.Y. was hospitalized again. He received red blood cell and platelet transfusions along with steroids, supplemental oxygen, and vancomycin for a *C. difficile* infection. *Id.* at 32-33.

On June 18, 2014, pediatric hematologist Dr. Sandhya Kharbanda recorded that S.Y. "seemed to have an autoimmune disease and he had a partial response to immunosuppressive therapy." Pet. Ex. 109 at 796. "Since his platelet count continue[d] to be low," Dr. Kharbanda and others at LPCH had previously recommended "curative therapy in the form of an allogeneic [donated] HSCT [hematopoietic stem cell transplant]." *Id.* at 796-77. This had been recommended previously but not offered due to S.Y.'s tenuous pulmonary status. *Id.* at 797. However, by June 2014, S.Y. was requiring significantly less supplemental oxygen and his lung function was improved. *Id.* Hematology, pulmonology, rheumatology, gastrointestinal, and other consulting teams concurred that S.Y. had become a good candidate for allogeneic HSCT. *Id.* This would involve a transplant of bone marrow as well as preserved umbilical cord blood from S.Y.'s younger brother (who was born in January 2014 and was determined to be a match for human leukocyte antigen). *Id.*

From June 20 – 27, 2014, S.Y. was hospitalized for increased jaundice. He received intravenous steroids. His planned stem cell transplant was put on hold due to his worsening hepatitis. Pet. Ex. 109 at 884-86. From July 23 – 25, 2014, S.Y. was hospitalized for fever. His blood and urine cultures were negative. Pet. Ex. 109 at 996-97.

Beginning in July 2014, S.Y. was seen by various providers at University of California San Francisco Medical Center (UCSF) regarding the possible transplant from his brother. *See generally* Pet. Ex. 7. A pediatric hematologist-oncologist agreed that this transplant was the only possible correction for S.Y.'s underlying autoimmune disorder. *Id.* at 5. He recommended administering "killed flu vaccine… as native flu would be very risky given his lungs." *Id.* at 75.

Due to concern about the progression of S.Y.'s liver disease following the possible transplant, a hepatologist (liver specialist) at UCSF was also consulted. *Id.* at 11. He wrote that the etiology of S.Y.'s transaminitis (high levels of certain liver enzymes, indicative of liver damage) was unclear but possibly autoimmune, infectious, or a result of drug toxicity. He recommended another liver biopsy to assess the etiology and degree of fibrosis, if any. However, a liver biopsy would need to be done "surgically in a controlled OR after optimizing

[16] The mother recalled during this extended period of hospitalization for S.Y., she was pregnant with her second child, S.Y.'s brother, who was born in January 2014. Pet. Ex. 10, ¶ 31.

plt [platelet] counts due to [S.Y.'s] risk of bleeding." *Id.* at 17. However, at a repeat appointment in August 2014, the hepatologist recommended against another liver biopsy because S.Y. "had a quite tenable and well recognized diagnosis of giant cell hepatitis with autoimmune hemolytic anemia," which was "most likely a humorally mediated one, unlike… the more common typical autoimmune hepatitis." He recommended another course of rituximab. *Id.* at 841-42, 1187.

A pulmonologist at UCSF wrote that S.Y. "did not have pulmonary hypertension on echocardiogram, nor does he have a known cardiac disease, so the etiology of his PVOD is unclear." *Id.* at 32. "The pulmonary complications of Evans syndrome are not well described in the literature." *Id.* The pulmonologist continued that S.Y.'s PVOD could be due to overall immune dysregulation which also led to his Evans syndrome; interstitial lung disease or pulmonary fibrosis secondary to drug toxicity (such as rituximab); or hepatopulmonary syndrome. *Id.*

In September 2014, a nurse practitioner in the hematology department at LPCH recorded the mother's request that they contact a doctor in Los Angeles, California who was "car[ing] for another Evans patient with giant cell hepatitis." Pet. Ex. 109 at 1215.

In October 2014, S.Y. began monthly IVIg. *See, e.g.*, *id.* at 1124, 1144, 1171-75, 1265. For three days in February 2015, he was hospitalized for dark urine concerning for hemolysis and increased respiratory difficulty. *Id.* at 1531-35. Between January to May 2015, he received several rounds of Velcade (bortezomib), which reduced or eliminated the blood plasma cells which produced autoantibodies. *Id.* at 1531-35, 1413. Following this treatment, S.Y. went into remission.

In October 2015, S.Y. had started transitional kindergarten but was being moved back to preschool due to his chronic medical condition and frequent hospitalizations, which had "interfered with his overall development." Pet. Ex. 108 at 31. But that month, S.Y. received his last known dose of Rituximab. *Id.* at 1413. He was also able to wean off supplemental oxygen during the day. *Id.* at 1463.

As of January 2016, S.Y. was still undergoing monthly IVIg. He remained on oxygen at night but did not require supplemental oxygen during the day. He was attending preschool. His mother reported that he was able to run around and play with other children and was "virtually indistinguishable from the other kids." Pet. Ex. 109 at 1388-89.

At the entitlement hearing in August 2017, the mother testified that S.Y. was still on oxygen at night, but not during the day. He was going to start first grade. His interaction with other children was limited due to the risk of infection. His platelets were higher than before, but not normal. His other blood counts were "much, much better." He was taking phloroglucinol (which the mother believed was an "anti-fungus for his lungs") and ursodiol (for his liver disease). Tr. 81-84. S.Y. continued to receive IVIg each month but no other immunosuppressants. Tr. 87. S.Y. was seeing his hematologist (at LPCH) once a month, his pulmonary doctor every three months, and his pediatricians every four months. Tr. 88.

3. *Loving* Prong Three: Did S.Y. experience significant aggravation of his condition?

This section will simply address whether S.Y.'s condition became markedly worse after the vaccinations at issue. To the extent to which the term "significant aggravation," as used in *Loving,* implies vaccine causation, that will not be addressed in this section. The role of the vaccinations, if any, in causing the change in S.Y.'s condition will be addressed below under *Loving* prongs five and six (*Althen* prongs two and three)).

In summary, the present case centers on Evans syndrome, an autoimmune condition in which antibodies cause significant reduction in blood cells. The experts noted cases in which just *one* cell line can be attacked, as in autoimmune thrombocytopenia (ITP) or autoimmune hemolytic anemia (AIHA). However, those diagnoses are usually acute and self-limiting.

Evans syndrome is considerably rarer. The first diagnostic requirement is bloodwork confirming the reduction of at least two cell counts, most often thrombocytopenia (platelets) and hemolytic anemia (red blood cells), but sometimes also neutropenia (neutrophils). The destruction of the different cell lines can occur simultaneously or sequentially. The second diagnostic requirement is a positive Coombs- or direct-antibody test, which shows that gammaglobulin is binding to the red blood cells, which confirms that the process is autoimmune. The diagnosis also depends on the exclusion of other autoimmune conditions. *See, e.g.*, Pet. Ex. 8 at 1-2; Resp. Ex. A at 4; Resp. Ex. D at 3 (internal citations omitted). "Although it is usually thought of as a childhood disease, it can also be present in adults." Resp. Ex. D at 3.

The parties and their experts agree that S.Y. had Evans syndrome prior to receiving the vaccines at issue. *See, e.g.*, Pet. Ex. 8 at 2 (Dr. Gershwin's initial report); Resp. Ex. A at 6 (Dr. Matloubian); Resp. Ex. D at 3 (Dr. Gill). As Dr. Gill explained at the hearing, Evans syndrome is typically not diagnosed until a patient presents with bruising, which prompts a blood test, which reveals the low blood counts. In this case, S.Y. was not suspected of having Evans syndrome. The primary care physician recorded the mother's history of one nosebleed which resolved on its own briefly. However, the mother did not report and the primary care physician did not observe bruising prior to the vaccinations. It just happened that the mother was anemic and was concerned that S.Y. was too. The mother requested bloodwork which was drawn approximately one hour after the vaccines were administered. The experts agreed that these vaccinations could not have impacted this bloodwork within such a short period of time. However, that bloodwork showed the destruction of at least two cell lines predating the vaccinations. Subsequently, a positive Coombs antibody test confirmed the diagnosis of Evans syndrome.

The parties also agree that after receiving the vaccinations, S.Y. experienced a very significant change in his condition including rash, fever, seizure, bruising, further drops in his blood counts, resistance to various treatments, positive ANA and antiphospholipid antibodies, PVOD, giant cell hepatitis, and consideration for a bone marrow transplant. There is no question that S.Y.'s condition became markedly worse in the time period after he received the vaccinations at issue. However, the extent to which that change, worsening or "significant aggravation" of S.Y.'s condition implies vaccine causation will not be addressed in this section. That will be addressed below under *Loving* prongs five and six (*Althen* prongs one and two).

4. *Loving* Prong Four (*Althen* Prong One): Petitioners have not established a reliable and reputable theory of how the flu, MMR, varicella, and/or Prevnar vaccinations can cause the significant aggravation of Evans syndrome.

Under this prong, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. It must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

In *Althen*, the Federal Circuit noted that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine,* the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen,* 418 F.3d at 1280 (emphasis added). Accordingly, the first *Althen* prong may be satisfied without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu*, 569 F.3d at 1378-79 (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d, 1317, 1325-26 (Fed. Cir. 2006)). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not from the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017). But this does not negate or reduce a petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C.*, 704 F.3d at 1356.

Petitioner's expert Dr. Gershwin opined that some persons are predisposed toward autoimmunity, which is characterized by what has been coined a Th-1 immune response. Pet. Ex. 8 at 3. At the entitlement hearing, Dr. Gershwin allowed that this opinion is based on surveys of large numbers of people; there is currently no blood or genetic test to detect this predisposition. *See* Tr. 17-19.

Dr. Gershwin opined that this predisposition toward autoimmunity is characterized by a bias toward a Th-1 immune response which is associated with the activation of proinflammatory cytokines, activation of T and B cells, and decrease in regulatory cells. Dr. Gershwin opined that an individual predisposed toward a Th-1 immune response is more likely to develop autoimmune disease. Over time, the body will try to restore immune tolerance - a balance between effector and regulatory components of the immune system – and will be better able to handle the increased cytokine activity associated with vaccination. Pet. Ex. 8 at 3; Pet. Ex. 11 at 1; Tr. 17-22.

However, Dr. Gershwin opined that there is a crucial early stage where the Th-1-predisposed immune system's cells are rapidly dividing and becoming more promiscuous. If a

treating physician is aware that a vulnerable person is in this stage, vaccinations should not be given. This is because vaccinations, by design, activate proinflammatory cytokines. It is impossible to develop an autoimmune response without cytokines. Pet. Ex. 8 at 2. They "drive inflammatory signals that regulate the capacity of resident and newly arrived phagocyte cells to destroy the invading pathogen… regulated antigen presentation function in dendritic cells and their migration to lymph nodes to initiate the adaptive immune response [and…] pla[y] a crucial role on the effector functions and homing properties of T and B cells, as well as their differentiation into memory cells." *Id.* at 3 (internal citations omitted).

Dr. Gershwin noted that cytokines activate a variety of cells. Approximately 10% of the activated cells are specific to the presenting antigen. The other 90% are non-specific "bystander" cells. Those are particularly geared to migrate toward inflammation. Pet. Ex. 8 at 2; Tr. 24-27.

Thus, in most cases, vaccines play a beneficial role in activating pro-inflammatory cytokines which help to create immunity and are then regulated back down to normal levels. *Id.* However, if a person is already predisposed to a Th-1 proinflammatory immune response and is in the early, active stage, vaccines can represent a further stimulus particularly activating the "bystander cells," causing autoimmune disease. Pet. Ex. 8 at 2, 4; Pet. Ex. 11 at 1, 5; Tr. 14.

Dr. Gershwin asserted that there was significant literature that illustrates the mechanism of bystander activation in both humans and experimental models. Pet. Ex. 11 at 2 (internal citations omitted). He specifically discussed studies where an animal with autoimmune disease is exposed to one antigen and then develops antibodies against various other antigens. *Id.*; Tr. 25-26. Dr. Gershwin noted that the clinical effect has been observed, but the pathways are still not understood.

Respondent's experts did not particularly respond to Dr. Gershwin's opinion that certain people are predisposed to Th-1 immune responses. Dr. Matloubian questioned whether autoimmunity has a crucial, early stage. Moreover: "In the case of an autoimmune process, it is not clear if there ever would have been an end to this response." Resp. Ex. C at 6-7.

Dr. Matloubian opined that we all have some autoreactive T cells. He acknowledged that "cytokine production, as a result of infection or vaccination, has been postulated to contribute to breakdown of tolerance and development of autoimmunity." Resp. Ex. A at 7. However, Dr. Matloubian opined that "there has not been convincing evidence that such mechanism is the prevailing pathway and the bystander hypothesis has fallen out of favor." *Id.* He cited an article by Wucherpfennig[17] for the proposition that limiting dilution analyses suggested that only a fraction of activated T cells in viral infections were actually virus-specific (as Dr. Gershwin opined, above). Resp. Ex. A23 at 3. However, techniques reveal that "the majority of activated T cells in viral infections are indeed antigen-specific." *Id.* at 3-4. "Since activation of native T cells requires signaling through the TCR [T cell receptor], it is unlikely that bystander activation is responsible for the *initial* activation of autoreactive T cells." *Id.* at 4 (emphasis added); *see also* Tr. 151-52. However, the next sentence reads: "Enhanced local cytokine production could,

[17] Wucherpfennig K.W., *Mechanisms for Induction of Autoimmunity by Infectious Agents*, 108 J. Clin. Invest. 1097 (2001) [Resp. Ex. A23].

however, lead to *further expansion* of *previously activated* T cells." *Id.* (emphasis added). Thus, the article still somewhat supports Dr. Gershwin's theory that an active autoimmune process could be amplified by cytokine production.

Regardless of the experts' opinions on bystander activation and autoimmune conditions generally, Evans syndrome is a *particularly* difficult autoimmune condition to evaluate. The available literature suggests that in Evans syndrome, the immune system responds to foreign antigen properly through the proliferation of B cells and T cells. However, because of some failure in the regulatory arm, the immune system is not returned to homeostasis. The activated immune cells continue to proliferate and attack the self. Some commentators have suggested that the regulatory defect lies in "a regulatory pathway in which activated immune cells express a cell surface protein called Fas ligand, which is recognized by T cells that possess a cell surface protein called Fas." *Bucci*, 2019 WL 1891809 at *19. However, the findings regarding this Fas-Fas ligand pathway seem at least paradoxical.[18] In the present case, Dr. Gershwin opined that Fas is a very interesting biomarker but it is not understood sufficiently to be useful in clinical medicine at this point. Tr. 48, 60. Neither of respondent's experts, Dr. Matloubian nor Dr. Gill, made any specific arguments regarding the possible role of the Fas-Fas ligand pathway.

Regardless, it is not well understood whether a trigger or other stimulus is necessary for the onset of Evans syndrome. I do not see any reference to whether any immune stimulus can be enough to trigger the failure of the regulatory immune system. Moreover, I do not see any reference to whether a particular stimulus from live virus(es) or vaccine(s) can heighten the dysregulated response resulting in a more debilitating course of this very rare condition.

Dr. Gershwin's theory of a predisposition toward autoimmunity characterized by a Th-1 pro-inflammatory response, further stimulation by vaccinations, and bystander activation may be plausible.[19] Respondent's experts essentially did not rebut this theory. However, Dr. Gershwin did not particularly relate this theory to Evans syndrome. Additionally, the sequence of events and the timing in S.Y.'s particular case are more key to the outcome. These will be addressed further below.

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[18] *Compare* Savaşan S. et al., *The Spectrum of Evans syndrome*, 77 Archives of Disease in Childhood 245 (1997) [Resp. Ex. D9] (in which 5/7 patients with Evans syndrome developed common variable immunodeficiency syndrome (CVID) which was attributed to *downregulation* of the Fas-Fas ligand pathway), *with* Teachey D.T. & Lambert M.P., *Diagnosis and Management of Autoimmune Cytopenias in Childhood*, 60 Pediatr. Clin. N. Am. 1489 (2013) [Resp. Ex. D10] (in which 7/12 patients with Evans syndrome were found to have autoimmune lymphoproliferative syndrome (ALPS) which was attributed to *upregulation* of the Fas-Fas ligand pathway); *see also Bucci*, 2019 WL 1891809 (discussing this at further length).

It should be noted that in the present case, the child has been diagnosed with Evans syndrome but never with either ALPS or CVID. This literature only stands for the proposition that Evans syndrome is not fully understood and has a significant degree of variation, possibly encompassing opposite immune responses (immune deficiency and immune over-proliferation).

[19] I have previously accepted Dr. Gershwin's opinion – supported in part by studies in animals - that prematurity, young infancy, and the alum adjuvant used in some vaccinations all together can skew an infant's immune system so far toward a *Th-2* response which is designed to fight against bacterial infection that it cannot mount a Th-1 response against viral infection. *Barrett v. Sec'y of Health & Human Servs.*, No. 14-137V, 2017 WL 4342334 (Fed. Cl. Spec. Mstr. Sept. 6, 2017), mentioned briefly during the entitlement hearing in *Berenji* at Tr. 20-21.

5. *Loving* Prongs Five and Six (*Althen* Prongs Two and Three): Petitioners have not established a logical sequence of cause and effect or a temporal association between S.Y.'s vaccinations and the significant aggravation of his condition.

To fulfill *Althen* prong two, a petitioner must show, by a preponderance of the evidence, "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen*, 618 F.3d at 1345. "A 'logical sequence of cause and effect' means what it sounds like—the claimant's theory of cause and effect must be logical." *Capizzano*, 440 F.3d at 1326. A petitioner is not required to eliminate all possible alternative causes of the injury. *See Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1150 (Fed. Cir. 2007) ("the Vaccine Act does not require the petitioner to bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case"). This standard permits the use of "circumstantial evidence" and accomplishes Congress's goal that "close calls regarding causation are resolved in favor of injured claimants." *Althen*, 165 F.3d at 1280. For example, while timing alone is not definitive, a physician may rely on the close temporal proximity between a vaccination and an injury in concluding that there is a logical sequence of cause and effect between the vaccine and the injury. *Capizzano*, 440 F. 3d at 1326.

In the present case, *Althen* prong two is linked with *Althen* prong three, under which a petitioner is required to establish a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation*." de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 543 (2011), *recons. den'd after remand,* 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *motion for review denied* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

i. Before Vaccinations

Dr. Gershwin applied the theory introduced above to opine that S.Y.'s October 17, 2011 vaccinations *did cause* the significant aggravation of his preexisting Evans syndrome. As noted above, Evans syndrome is understood to be an autoimmune condition. Dr. Gershwin opined that autoimmunity is characterized by a bias toward a Th1 pro-inflammatory response and that existed in S.Y. Tr. 16-17.

Dr. Gershwin opined that when S.Y. received the vaccines, he was developing Evans syndrome. S.Y. was "in the incipient or beginning active phase of an immunological storm." Pet. Ex. 11 at 2; *see also* Pet. Ex. 8 at 2. His immune cells were in the expansion phase, rapidly

dividing, and becoming further biased toward autoimmunity. Tr. 14, 38-39, 43. In his reports, Dr. Gershwin did not explain the basis for these statements.

At the hearing, Dr. Gershwin opined that the onset of Evans syndrome was probably about 7 - 14 days before the vaccinations. He did not have significant symptomatology beforehand. The only clue was a nosebleed approximately one week prior. Tr. 11-12, citing Pet. Ex. 2 at 869 (October 18, 2011 medical record of history given by S.Y.'s mother). This helped to place the onset of immunothrombocytopenia which was confirmed by bloodwork. Tr. 11-12, 31, citing Pet. Ex. 4 at 56 (October 17, 2011 platelet count of 17,000/uL (low, compared to reference range of 150,000 – 400,000/uL)). Dr. Gershwin opined that the lifespan of a platelet is approximately eight or nine days. Tr. 11.

Dr. Gershwin also opined on the day of the vaccinations, October 17, 2011, S.Y. already had hemolytic anemia evidenced by the hematocrit level of 31% (low, compared to reference range of 33.0 – 43.5%). Pet. Ex. 4 at 57. By October 28, 2011, hematocrit decreased to 26.9%. Pet. Ex. 2 at 887. S.Y.'s reticulocytes also rose. Those apparently were not measured on the date of vaccination. Pet. Ex. 4 at 57. They were at 1.8 Hcf on October 18 (one day after the vaccinations) and rose to 8.2 Hcf by November 4. Pet. Ex. 2 at 776, 884 (comparing to a reference range of 0.5 – 1.5 Hcf). Pet. Ex. 2 at 884. Dr. Gershwin explained that reticulocytes are larger, younger red blood cells produced by the bone marrow. They tend to be produced in response to hemolytic anemia. Dr. Gershwin opined that these blood counts were further evidence that S.Y.'s Evans syndrome "wasn't there a year ago." The disease was just beginning to develop and was in a "crescendo phase" when the vaccinations were given. Tr. 31-34. The additional immune challenge posed by the vaccinations, including at least fourteen antigens, caused a flare of his disease which led to further dysregulation and loss of tolerance. Tr. 13-14, 33.

In contrast, respondent's experts Dr. Gill and Dr. Matloubian disagreed that S.Y.'s illness was just beginning when he received the vaccines. Dr. Gill opined that the onset of immunothrombocytopenia can be "insidious" and it can develop for several months before manifesting in visible bleeding or bruising, which S.Y. was reported to have approximately one week before the vaccinations. Tr. 99-105. On cross-examination, Dr. Gill stated that it is difficult to detect the start of an autoimmune process, but it would take at least a month for platelets to drop down to the level S.Y. had on the day of the vaccinations. Tr. 141-42. Dr. Matloubian agreed that it would have taken at least a month for the platelets to drop to the level found in S.Y. Tr. 142.

Respondent's expert Dr. Gill noted that by October 19, 2011, S.Y. had a positive Coombs test which was evidence of IgG antibodies (but not IgM antibodies). Tr. 104-05 (discussing Pet. Ex. 2 at 870). Dr. Gill opined that this was further evidence that S.Y.'s Evans syndrome was not "just beginning," but had been developing for some time. Tr. 104-05.

Dr. Matloubian opined that the Coombs test demonstrated that when S.Y. received the vaccinations, there were already IgG antibodies present, which were coating the red blood cells and possibly the platelets. Tr. 159, 220. Dr. Matloubian focused on the question of: "Where do these antibodies come from and who makes them?" *Id.* Dr. Matloubian stated that B cells need to activate, proliferate, go through the germinal center, then differentiate into plasma cells which

go to the bone marrow, where they make antibodies. The entire process takes at least 10 – 14 days but is difficult to track precisely. Tr. 159-60. Dr. Matloubian suggested that T cells are also involved to some extent, but they cannot be detected without a very specialized test which was not done in S.Y.'s case. Tr. 231.

On cross-examination, Dr. Matloubian agreed that S.Y.'s platelets were already low, but after the vaccinations, there was a "significant drop." However, antibodies were already in production and were coating the platelets. The character of the autoimmunity did not change following the vaccinations. The only difference was that more of the platelets were "mopped up." Tr. 228-29.

On redirect, Dr. Gershwin opined that 7 – 14 days is about the time that it takes for a class switch from IgG to IgM. Tr. 194. Therefore, the experts agreed that we don't know for sure when the class switch occurred, just that there were IgG cells present on the Coombs direct test when it was performed. Tr. 105.

Dr. Gershwin said that ultimately, it did not matter whether S.Y. had been developing Evans syndrome for 7 days, 14 days, or a month when the vaccines were administered. But it was an early, active, disease which had not begun "months in the past." Tr. 233-34.

ii. Short-Term Course

I find that there is preponderant evidence that the vaccines, specifically MMR vaccine, caused a short-term adverse response including rash centered at the vaccination site, fever, and seizures in late October 2011. Several different treating physicians offered this opinion. *See, e.g.*, Pet. Ex. 2 at 473 (neurologist Dr. Olson); 765 (pediatrician Dr. Wong); 785 (immunologist Dr. Lewis, noting a CDC study linking MMR vaccines with febrile seizure); 856 (infectious disease specialist Dr. Dyner); 863 (hematologist-oncologist Dr. Duda). Petitioner's expert Dr. Gershwin also opined that the vaccinations activated pro-inflammatory cytokines which resulted in fever, which caused the seizures. Tr. 30.

Respondent's expert Dr. Matloubian opined that "the vaccines that [S.Y.] received on October 17, 2011, and more specifically, the MMR vaccine, may have led to the febrile illness and hospitalization shortly after on October 28, 2011." Resp. Ex. A at 3. Similarly, Dr. Gill opined that: "About 5 percent of children who receive the MMR are known to have fevers following vaccination." Tr. 100. That might also explain S.Y.'s acute episode including fever and rash. *Id.*

It is probable that the vaccines activated S.Y.'s immune system including the production of pro-inflammatory cytokines which caused the rash centered at the vaccination site, fever, and seizures, consistent with Dr. Gershwin's testimony. This was not rebutted by respondent's experts and was in fact suggested by several treating physicians.

However, those same treating physicians also noted that S.Y.'s adverse response to the vaccines *only* involved the rash, fever, and seizures in October 2011. Pet. Ex. 2 at 473, 765, 785,

856, 863.[20] This resolved quickly, within approximately one month. *See, e.g.*, Pet. Ex. 2 at 863 (November 10, 2011 note by Dr. Duda that "his apparent vaccine-related illness has since resolved"); *id.* at 714-718 (December 2011 hospital record lacking any observation of rash, fever, or bruising).

The treating physicians did not suggest that the vaccines caused or aggravated S.Y.'s Evans syndrome. They agreed that was a separate process which existed before and continued on its typical course afterward, regardless of the vaccines. The course of S.Y.'s Evans syndrome will be addressed further below.

iii. Long-Term Course

As made clear above, S.Y. had Evans syndrome before receiving the vaccinations at issue on October 17, 2011. After receiving the vaccinations, he developed rash, fever, and seizures which were attributed to the vaccines and also resolved within approximately one month.

Additionally, after receiving the vaccinations, S.Y. experienced a significant aggravation of his Evans syndrome. He developed visible bruises. His blood counts dropped shortly after the vaccinations and at numerous later occasions despite treatment with multiple immunosuppressants. As a result of those immunosuppressants, he developed various infections. In February 2012, he was given Rituximab which wiped out his B cells. In 2013, S.Y. developed PVOD, anti-nuclear antibodies, anti-phospholipid antibodies, and giant cell hepatitis.

The key question is whether this course was *logically caused* by the vaccinations, and *not* simply consistent with the course of Evans syndrome if the vaccinations had not been given. *See, e.g.*, *Locane*, 685 F.3d 1375 (affirming that a petitioner exhibited the natural course of Crohn's disease, which therefore was not a significant aggravation caused by Hepatitis B vaccinations); *Hennessey*, 91 Fed. Cl. 126 (affirming the special master's opinion including that the petitioner "failed to establish any logical connection between his Hepatitis B vaccinations and his T1D [type 1 diabetes]" and that his deteriorated condition was caused by "the natural progression of insulin dependence, rather than his vaccines").

In this case, petitioner's expert Dr. Gershwin acknowledged that S.Y. had Evans syndrome before and he would have continued to have that condition regardless of the vaccinations on October 17, 2011. However, Dr. Gershwin opined that without those vaccinations, S.Y.'s Evans syndrome "would have been more benign and he should have recovered more likely than not within a period of 40 months following diagnosis." Pet. Ex. 12 at 2. Dr. Gershwin opined that but for the vaccinations, S.Y. would have had a less severe course. He would have shown improvement after receiving IVIg and maybe one other immune

[20] It should be noted that S.Y. did experience some further seizures. Specifically, more than six months later after the vaccinations and the initial adverse response, in April 2012, S.Y. was started on cyclosporine (an immunosuppressant). Then, in June 2012, S.Y. had two separate seizure episodes. Those were attributed to the cyclosporine, which was discontinued. S.Y. was started on Keppra. Pet. Ex. 2 at 474, 456-57; Pet. Ex. 3 at 1-54; Pet. Ex. 5 at 936. He also had seizure activity during a hospitalization for pulmonary veno-occlusive disease ("PVOD") in March 2013. Pet. Ex. 2 at 98-99, Pet. Ex. 5 at 133-42.

suppressant. His condition possibly would have waxed and waned, but it would not have had so many relapses and complications.

Dr. Gershwin opined that because of the vaccinations, S.Y. experienced a course of Evans syndrome that was much more severe than what is experienced by other children with Evans syndrome. In particular, S.Y.'s lack of response to numerous treatments; the recommendation of a bone marrow transplant; and his development of anti-nuclear antibodies, antiphospholipid antibodies, hepatitis, and PVOD were unusual for Evans and were instead due to the contributions of the vaccinations. Dr. Gershwin opined that he could not find cases like this in the literature. Pet. Ex. 8 at 2, 4; Pet. Ex. 11 at 5; Pet. Ex. 12 at 1-2; Tr. 13-15, 35-36, 46, 235.

Dr. Gershwin specifically cited a study on 156 patients under 18 years old that were diagnosed with Evans syndrome throughout France who were followed for a median of 6.8 years. Dr. Gershwin emphasized that of the 71 patients with "simultaneous" Evans syndrome (involving both immunothrombocytopenia and hemolytic anemia at the same time), there were no patients "who developed giant cell hepatitis and indeed the majority of patients had a benign outcome, i.e., more than 50% had a relapse-free survival with respect to both thrombocytopenia and hemolytic anemia." Pet. Ex. 12 at 1.[21]

Dr. Gershwin did find two case reports of patients with Evans syndrome developing giant cell hepatitis, but he suggested that the first case was related to a liver transplant and the other was suggestive of a "common immune dysregulation mechanism." Pet. Ex. 12 at 2.[22]

Respondent's experts disagreed that S.Y. had an unusually severe course of Evans syndrome. Dr. Gill opined that Evans syndrome is a "chronic and relapsing condition that is often refractory to therapy with IVIg, corticosteroids, and splenectomy; responses to other agents have been anecdotal and inconclusive." Resp. Ex. D at 3.[23] She asserted that other patients with Evans syndrome who do not receive vaccinations and are receiving various immunosuppressant therapies still have recurrences of thrombocytopenia and hemolytic anemia. She opined that patients with Evans syndrome often develop other autoimmune phenomena. Resp. Ex. D at 3; *see also* Tr. 96-97, 110, 113-17. For example, Mathew et al.[24] reported data collected from pediatric hematologists primarily in the United States and Canada on 42 pediatric patients with Evans syndrome, who were followed for a median of 3 years (with a range of 4 months – 18.9

[21] Aladjidi N. et al., *Evans syndrome in Children: Long-Term Outcome in a Prospective French National Observational Cohort,* doi: 10.3389/fped.2015.0079 [Pet. Ex. 15]; *see also* Aladjidi N. et al., *New Insights into Childhood Autoimmune Hemolytic Anemia: A French National Observational Study of 265 Children,* 96 Haematologica 655 (2011) [Pet. Ex. 16].

[22] *Citing* Yokoyama S. et al., *Evans syndrome after Successful Living-Donor Liver Transplantation for Neonatal Giant Cell Hepatitis*, 84 Transplantation 798 (2007) [Pet. Ex. 106]; Hadzic N. et al., *Coombs-positive Giant Cell Hepatitis – A New Feature of Evans syndrome*, 78 Arch. Dis. Child. 397 (1998) [Pet. Ex. 107].

[23] Citing Mathew P. et al., *Evans Syndrome: Results of a National Survey*, 19 J. Ped. Hem. Onc. 433 (1997) [Pet. Ex. 58, also at Resp. Ex. D5].

[24] Citing Mathew P. et al. [Pet. Ex. 58].

years). Most of the patients had a chronic course; 20 (48%) had active disease and remained on treatment at the end of the follow-up period. Some were reported to develop other autoimmune conditions including lupus, which is not considered a true Evans syndrome, but the specifics of the autoimmune diseases were not mentioned. Pet. Ex. 58, *discussed at* Tr. 132.

Additionally, Al Ghaithi et al.[25] reported data from several Canadian hospitals on 23 pediatric patients with Evans syndrome and other multi-lineage cytopenias who were followed for a median of 5 years (with a range of 2 months – 12 years). Rates of remission were low, with all cytopenias resolving in only 3 patients (13%). More than half of the 23 patients were found to have underlying immune deficiencies including Common Variable Immune Deficiency (CVID), autoimmune lymphoproliferative disorder (ALPS), and combined immunodeficiency (CID).[26] The article indicated that 26% of the studied patients developed other non-hematological autoimmune disease but did not specify which ones. Dr. Gill contended that the article demonstrates that Evans syndrome is not just a combination of ITP and HA but is a chronic disease that can involve other organs. Tr. 112.

Dr. Gill correctly noted that Evans syndrome is particularly rare. The published studies are generally retrospective and involve small cohorts. They suggest that Evans syndrome is chronic and often refractory to treatment with ongoing relapses most often involving low platelets. These articles make occasional reference to the development of other autoimmune conditions but are not specific.[27]

Dr. Gill believed that S.Y.'s course was "consistent with" and "very similar" to other patients with Evans syndrome and was unrelated to vaccinations. Resp. Ex. D at 4; Tr. 96. She stated that she had treated one patient with chronic ITP who developed autoimmune hepatitis in the absence of vaccination. She has never seen a patient with Evans syndrome and PVOD. Tr. 137-38. She ultimately testified that it was "very unlikely" that S.Y.'s vaccinations caused the development of PVOD 16 months later or autoimmune hepatitis 22 months later (also discussed by Dr. Matloubian, as addressed below). Tr. 96.

Dr. Matloubian agreed with Dr. Gill's opinion that Evans syndrome is chronic, resistant to various treatments, and associated with various other autoimmune phenomena. Dr. Matloubian provided several additional reports of autoimmune hepatitis occurring in association with Evans syndrome or either ITP or hemolytic anemia. Resp. Ex. A at 6[28]; *see also* Pet. Ex.

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[25] Al Ghaithi I.A. et al., *Combined Autoimmune Cytopenias Presenting in Childhood*, 63 Pediatr. Blood Cancer 292 (2016) [Resp. Ex. D4].

[26] S.Y. was not diagnosed with any of these conditions.

[27] *See, e.g.*, Aladjidi N. et al. [Pet. Ex. 15]; Miller B.A. & Beardsley D.S. [Resp. Ex. D7]; Wang J.D. *Acute Immune Thrombocytopenia Purpura in Infants: Associated Factors, Clinical Features, Treatment and Long-Term Outcome*, 77 Eur. J. Haematol. 334 (2006) [Resp. Ex. D12]; Savaşan S. et al. [Resp. Ex. D9]; Teachey D.T. & Lambert M.P. [Resp. Ex. D10].

[28] Maggiore G. et al., *Giant Cell Hepatitis with Autoimmune Hemolytic Anemia in Early Childhood: Long-Term Outcome in 16 Children*, 159 J. Pediatr. 127 (2011) [Resp. Ex. A15]; Carey E.J. et al., *Successful Rituximab Treatment in Refractory Autoimmune Hepatitis and Evans syndrome*, 139 Rev. Med. Chil. 1484 (2011) [Resp. Ex. A16]; Korkmas H. et al., *Autoimmune Hepatitis-Primary Biliary Cirrhosis Overlap syndrome concomitant with Immune Hemolytic Anemia and Immune Thrombocytopenic Purpura (Evans syndrome)*, 37 Clin. Res. Hepatol.

109 at 1215 (September 2014 LCPH medical record noting the mother's request that S.Y.'s treating physicians contact a doctor in Los Angeles who was "car[ing] for another Evans patient with giant cell hepatitis"). Dr. Matloubian suggested that autoimmune hepatitis is one biological manifestation of Evans syndrome and other autoimmune hematological diseases and is not related to vaccinations. Resp. Ex. A at 6; Resp. Ex. C at 8.

Dr. Matloubian also argued that there was not a logical sequence of cause and effect between the vaccinations and S.Y.'s later course. Specifically, if S.Y. were experiencing an "immunological storm" that was exacerbated by the vaccinations, resulting in a break of tolerance, Dr. Matloubian would have expected the manifestations of autoimmune disease to develop within a short period of time such as a few months, rather than a year later. Resp. Ex. A at 3, 5-9; Resp. Ex. C at 6.

Dr. Matloubian also emphasized that in February - March 2012, S.Y. received Rituximab which depletes B cells. Dr. Matloubian estimated that Rituximab wiped out 99% of the B cells that were present when S.Y. received the vaccinations. Following the treatment with Rituximab, S.Y.'s bone marrow then produced new replacement B cells which were observed in February 2013. Only afterward did S.Y. become positive for antinuclear (ANA) antibodies and antiphospholipid antibodies and developed PVOD and giant cell hepatitis. Dr. Matloubian opined that the activation of these new B cells and the development of these sequelae more than one year after the vaccinations cannot be attributed to the same. Tr. 164-69; *see also* Resp. Ex. C at 7.

Dr. Matloubian also noted that in early 2015, S.Y. received Velcade, which eliminated the plasma cells which produce antibodies. Afterwards, S.Y. finally went into remission. Although the administration of Velcade was successful in treating S.Y.'s Evans syndrome, it also wiped out his preexisting immunity, therefore he has continued to receive IVIg to prevent further infection. Tr. 208-11.

Dr. Matloubian agreed with Dr. Gershwin that autoimmune hematologic diseases, particularly Evans syndrome, are not fully understood. He believed that a genetic defect was involved in S.Y.'s Evans syndrome and other long-term conditions. Resp. Ex. C at 8; Tr. 174, 182. However, no specific genetic cause has been identified in S.Y.'s case. Pet. Ex. 5 at 375-76.

iv. Conclusion

In conclusion, there can be little question that S.Y.'s condition became markedly worse after receiving the vaccines on October 17, 2011. His treating doctors generally thought that the process including fever, seizure and full body rash were likely attributable to the vaccine. However, that short-term injury, if attributed to the vaccines, did not last for more than six

Gastroenterol. e45 (2013) [Resp. Ex. A18]; Palaniappan S. & Ramanaidu S., *A Rare Case of Autoimmune Hepatitis Overlapping with Autoimmune Hemolytic Anemia and Immune Thrombocytopenic Purpura in a Male Patient*, 67 Med. J. Malaysia 326 (2012) [Resp. Ex. A19]; Raj S. et al., *Giant Cell Hepatitis with Autoimmune Hemolytic Anemia: A Case Report and Review of Pediatric Literature*, 50 Clin. Ped. 357 (2011) [Resp. Ex. A20]; Shores D. et al., *Giant Cell Hepatitis and Immune Thrombocytopenic Purpura: Reversal of Liver Failure with Rituximab Therapy*, 55 J. Pediatr. Gastroenterol. Nutr. e128 (2012) [Resp. Ex. A21].

months.[29] It is significantly more difficult to find a logical and temporal association between S.Y.'s vaccinations and his long-term course which is at least somewhat similar to other patients with Evans syndrome. The available literature on this very rare disease suggests that Evans syndrome is chronic and refractory to treatment. S.Y.'s development of antinuclear antibodies, antiphospholipid antibodies, hepatitis, and PVOD seems particularly rare. However, those conditions are unlikely to be caused by B cells stimulated by the vaccines, which were eliminated and replaced in the intervening time period. Thus, there is not a logical sequence of cause and effect or an acceptable temporal association between the vaccinations and S.Y.'s long-term course.

IV. Conclusion

I wish to extend my sympathy to S.Y. and his family in light of the enormous suffering they have experienced in association with his Evans syndrome. Unfortunately, I cannot conclude that the vaccines S.Y. received in October 2011 caused or substantially contributed to the long-term evolution of this condition. Accordingly, petitioners' claim must be and is hereby **DISMISSED.** In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of the Court is directed to enter judgment forthwith.[30]

IT IS SO ORDERED.

s/ Thomas L. Gowen
Thomas L. Gowen
Special Master

[29] *See* Section 11(c)(1)(D)(i) (providing that a petitioner bears the burden of establishing "residual effects or complications of the illness, disability, injury, or condition for more than six months after the administration of the vaccine").

[30] Entry of judgment is expedited by each party's filing notice renouncing the right to seek review. Vaccine Rule 11(a).